DETAILED ACTION

Claims 1-4, 7-12, 16-25, 32, 33, 38 and 40 are pending in the application.

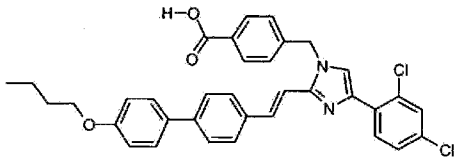
The finality of the previous Office Action dated January 7, 2008 is withdrawn. At the request of Applicant, the Supplemental Amendment filed May 1, 2008, not the Amendment filed April 17, 2008, will be entered.

Election/Restrictions

Applicant's election with traverse of Group III (claims 1-46), and the species of Example 320 found on page 287 of the instant specification (reproduced below), in the reply filed on October 27, 2006 was acknowledged in a previous Office Action.

The structure given in the election was actually the structure of Example 320, as stated by Applicant in the Remarks section of the Amendment filed June 18, 2007.

Example 320



4-[2-[2-(4'-butoxy-biphenyl-4-yl)-(E)-vinyl]-4-(2,4-dichloro-phenyl)-imidazol-1-ylmethyl]-benzoic acid

The claims within elected Group III and the Information Disclosure Statements were examined to the extent that they are readable on the elected species of Example 320. Since no prior art was found on the elected species, the examination was expanded within elected Group III until art was found, in which case, the examination stopped and art has been applied against the claims. Note, M.P.E.P. § 803.02. The

subject matter of the expanded search (inclusive of the elected species of Example 320) is as follows:

W is $N(R_2)$;

Ar_1 is an optionally substituted phenyl;

Ar_2 is an optionally substituted phenyl;

T is an optionally substituted phenyl;

L_2 is a direct bond; and

all other variables are as defined.

The claims that are embraced by the subject matter of the expanded search are claims 1-46. The requirement was deemed proper and therefore made FINAL in a previous Office Action.

Subject matter not embraced by the above indicated expanded search are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention(s), there being no allowable generic or linking claim. Applicant timely

traversed the restriction (election) requirement in the reply filed on October 27, 2006.

Rejections made in the previous Office Action that do not appear below have been overcome by Applicant's amendments to the claims. Therefore, arguments pertaining to these rejections and objections will not be addressed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 7-12, 16-25, 32, 33, 38 and 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a

pharmaceutically acceptable salt or prodrug thereof of a compound of formula (I), does not reasonably provide enablement for a solvate of a compound of formula (I). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in making an enablement rejection are summarized as:

a) the quantity of experimentation necessary,

b) the amount of direction or guidance presented,

c) the presence or absence of working examples,

d) the nature of the invention,

e) the state of the prior art,

f) the relative skill of those in the art,

g) the predictability or unpredictability of the art, and

h) the breadth of the claims.

In re Colianni, 195 USPQ 150 (CCPA 1977). *In re Rainer*, et al., 146 USPQ 218 (CCPA 1965). *Ex parte Formal*, 230 USPQ 546 (BPAI 1986).

a) Determining if a particular compound would form a solvate would require synthesis and recrystallization of the compound solvate using a variety of solvents, temperatures and humidities. The experimentation for solvates is potentially open-ended.

b) The specification merely mentions the Applicant's intention to make solvates, without teaching the preparation thereof.

c) While the claims recite solvates, no working examples show their formation. As stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190, 1194 (Fed.Cir. 1993):

> The specification purports to teach, with over fifty examples, the preparation of the claimed compounds ... However ... there is no evidence that such compounds exist ... [T]he examples ... do not produce the postulated compounds ... [T]here is ... no evidence that such compounds even exist.

The specification shows no evidence of the formation and actual existence of solvates. Hence, Applicant must show formation of solvates or limit the claims accordingly.

d) The nature of the invention is chemical synthesis of solvates, which involves chemical reactions.

e) The state of the art recognizes that the formation, composition and therapeutic activity of solvates is unpredictable. The Federal Circuit has recognized a solvate as an example of a polymorph or pseudopolymorph (emphasis added):

> "Polymorphs" are distinct crystalline structures containing the same molecules. <u>These structural differences can affect various properties of the crystals</u>, such as melting points and hardness (e.g., graphite and diamonds are both crystalline forms of carbon) .... [P]seudopolymorphs are often loosely called polymorphs ... Pseudopolymorphs not only have their molecules arranged differently but also have a slightly different molecular composition. A common type of pseudopolymorph is a solvate, which is a crystal in which the molecules defining the crystal structure "trap"

> molecules of a solvent. The crystal molecules and the solvent molecules then bond to form an altered crystalline structure.

SmithKline Beecham Corp. v. Apotex Corp., 74 USPQ2d 1398, 1409 (Fed.Cir. 2005). The same rationale obtains for hydrates; solvates in which the solvent is water. Souillac, et al., Characterization of Delivery Systems, Differential Scanning Calorimetry, pages 217-218 (in Encyclopedia of Controlled Drug Delivery, 1999, John Wiley & Sons, pages 212-227), recognize that different polymorphs of the same drug can have different therapeutic activity (emphasis added):

> Because different polymorphic forms of the same drug exhibit significant differences in their physical characteristics, therapeutic activity from one form to another may be different. Studying the polymorphism of a drug and the relative stability of the different polymorphs is a critical part of pre-formulation development.

Further, Vippagunta et al. (Advanced Drug Delivery Reviews, 48 (2001), pages 3-26) state "Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated in

to the crystal lattice of a compound is complex and difficult." See page 18, section 3.4.

f) The artisan using Applicant's disclosure to prepare the claimed solvates would be, e.g., an experienced process chemist with at least a BS chemistry degree.

g) Chemical reactions are known as unpredictable. *In re Marzocchi, et al.*, 169 USPQ 367, 370 (CCPA 1971); *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). See above regarding the unpredictability of solvate formation.

h) The breadth of the claims includes thousands of compounds of the instant formula (I) as well as presently unknown compounds embraced by the terms solvates. See MPEP 2164.01(a), discussed supra, justifying the conclusion of lack of enablement commensurate with the claims. Undue experimentation will be required to practice Applicant's claimed invention.

Claims 32, 33, 38 and 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for alleviation of one or more symptoms resulting (see page 323, lines 20-23) from type I and type II diabetes, obesity and psoriasis, does not reasonably provide enablement for the treatment of type I and type II diabetes, obesity and psoriasis wherein treatment embraces the outright cure of the disorder or prevention of the onset of the disorder (see page 323, lines 22-24). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,

2. the state of the prior art,

3. the predictability or lack thereof in the art,

4. the amount of direction or guidance present,

5. the presence or absence of working examples,

6. the breadth of the claims,

7. the quantity of experimentation needed, and

8. the level of the skill in the art.

The nature of the invention

Applicant is claiming a pharmaceutical composition comprising a compound of formula (I) which is sufficient to treat type I and type II diabetes, obesity and psoriasis. See, for example, instant claim 32. From the reading of the specification, it appears that Applicant is asserting that any compound, because of its mode of action which acts as a protein tyrosine phosphatase (PTPase) inhibitor, would be useful for the prevention or curing of type I and type II diabetes, obesity and psoriasis.

The state of the prior art and the predictability or lack thereof in the art

For example, the state of the art is that the prevention of diabetes remains highly unpredictable. Colagiuri et al. {American Journal of Public Health, September 2006, Vol. 96, No. 9, pages 1562-1569} state "Type 2 diabetes is a complex metabolic disorder triggered by lifestyle factors superimposed on a genetic predisposition." Colagiuri et al. also state "Although we recognize the benefits of science, surgery, and service delivery in relation to certain aspects of chronic disease prevention, it is clear that, either independently or in concert, none can achieve the broad scale changes required to prevent diabetes and obesity on a population basis."

According to Bruno et al. {Expert Opinion Emerging Drugs, (2005), 10(4), pages 747-771}, diabetes mellitus is a major health problem that affects over 170 million people worldwide. Park {Diabetes Research and Clinical

Practice 66S (2004), S33-S35} states current methods of treating diabetes is inadequate and that current strategies to prevent type 2 diabetes mellitus are based on efforts to reduce insulin resistance and to preserve or increase pancreatic beta cell function in high risk individuals. Park also states, "It appears that multiple genes with weak effect are involved in the development of type 2 diabetes mellitus which makes searching diabetogenic genes more complicated." Curtis et al. {The Journal of the American Board of Family Practice, Vol. 18, pages 37-43, (2005)} state "there is much yet to learn about preventing type 2 diabetes". From Curtis et al., it is clear that there are currently no medications on the market that have been successful in the prevention of diabetes.

The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The amount of direction or guidance present and the presence or absence of working examples

There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the diseases claimed in the pharmaceutical compositions. That a single class of compounds can be used to prevent or cure the diseases stated in the claims is an incredible finding for which Applicant has not provided persuasive supporting evidence.

The breadth of the claims

The breadth of the claims is a pharmaceutical composition for sufficient to treat type I and type II diabetes, obesity and psoriasis.

The quantity of experimentation needed

The nature of the pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities for each of the diseases instantly claimed

in the composition. The quantity of experimentation needed would be undue when faced with the lack of testing, and when faced with the unpredictability of the pharmaceutical art. Thus, factors such as "sufficient working examples", "the level of skill in the art" and predictability, etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims.

The level of the skill in the art

Even though the level of skill in the pharmaceutical art is very high, based on the unpredictable nature of the invention and state of the prior art, one skilled in the art could not use the claimed invention without undue experimentation.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura L. Stockton whose telephone number is (571) 272-0710. The examiner can normally be reached on Monday-Friday from 6:15 am to 2:45 pm. If the

examiner is out of the Office, the examiner's supervisor, Joseph McKane, can be reached on (571) 272-0699.

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The Official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

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